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REVIEW ARTICLE

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The roles of immuno-modulator treatment and echocardiographic screening in rheumatic fever and rheumatic heart disease control: research from Aotearoa, New Zealand*

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ABSTRACT

This review summarises advances in research from Aotearoa, New Zealand (NZ) that have potential to reduce the inequitable distribution of acute rheumatic fever (ARF) and rheumatic heart disease (RHD). ARF incidence and RHD prevalence are unacceptably inequitable for Māori and Pacifica. Recent qualitative research has demonstrated mismatches between the lived experience of those with ARF/RHD and health service experience they encounter.

NZ-led research has contributed knowledge to all stages of disease prevention (primordial, primary and secondary) and for tertiary management. Modifiable risk factors for ARF are racism across health sectors, household crowding, barriers to accessing primary health care, a high intake of sugar-sweetened beverages and preceding sore throat and skin infections. NZ research has evaluated the impact of a large-scale sore throat management programme and Streptococcal A vaccine development.

This review highlights two programme domains of research by the authors that have the potential to reduce the burden of chronic RHD: firstly, effective immunomodulation of ARF to reduce the severity of carditis, with current clinical trials of hydroxychloroquine in NZ; secondly, the development

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of echocardiographic screening of previously undetected RHD. This now meets criteria for an effective screening test and has potential translation for disease control of RHD.

Introduction

Acute Rheumatic Fever (ARF) is an autoimmune sequela to Group A *beta-haemolytic streptococcus* (Strep A) infection that most commonly affects children. The most serious clinical manifestation of ARF is carditis, which can progress to chronic Rheumatic Heart Disease (RHD) characterised by ongoing valve damage without additional Strep A infection.

The previous global disease burden estimate for RHD of 40 million cases (Roth et al. 2020) has recently been revised to 46 million cases (David Watkins, personal communication), with over 398,000 deaths per year (Vaduganathan et al. 2022). Despite this, there is evidence of significant underfunding for RHD research in comparison to other infectious diseases with chronic disease outcomes (Macleod et al. 2019).

In comparison, the burden of ARF and RHD are numerically small, yet unacceptably high for a high-income country, with approximately 150 cases of ARF per year and 5000 prevalent cases of severe RHD in Aotearoa, New Zealand (NZ) (New Zealand Heart Foundation 2014; Tilton et al. 2022). There are huge inequities by ethnicity, with Māori and Pacific peoples disproportionately affected (New Zealand Heart Foundation 2014; Burgess 2016; Jack et al. 2018; Anderson et al. 2019; Bennett et al. 2021b; Tilton et al. 2022; Trace 2022).

In 2018, a NZ-led submission to the World Health Assembly adopted resolution WHA 71.14, which called for the World Health Organization (WHO) to launch a coordinated 'multi-faceted' global response to RHD and ARF (White 2018; WHO 2018).

Disease control of ARF and RHD: There are many recognised aspects to prevention and control of ARF and RHD, which span the disease pathway: primordial and primary prevention of group A streptococcal (Strep A) infections (Jack et al. 2018; Bennett et al. 2021b; Wyber et al. 2021a); secondary ARF/RHD prophylaxis; and tertiary management of RHD (Carapetis et al. 2016). Here, we summarise some of New Zealand's research contribution along this continuum.

Lived experience: Over-riding all aspects of improved control should be the recognition of the lived experience of those with ARF and RHD. In Aotearoa, New Zealand, several studies stemming from 2016 to the present have investigated the lived experiences of Māori and Pacific Peoples with ARF and RHD and their whānau (family), with a focus on service engagement through the diagnosis and management of their conditions. Sadly, these studies consistently demonstrated mismatches between the expectations and complex living conditions of those with ARF/RHD and the service experiences they encounter (Burgess 2016; Anderson et al. 2019; Trace 2022). Barriers to accessing health care were similar across the diagnostic and health management pathways for patients and families, where geographic, economic and social barriers resulted in delayed diagnosis of streptococcus infections or rheumatic fever and missed secondary prophylaxis or echocardiography appointments. In some cases, these barriers and delays resulted in recurrences of ARF (Anderson et al. 2019).

Service design and delivery: Health systems' ability to provide high-quality, culturally safe and meaningful relationships with the people whom they serve is one of the most powerful predictors of health outcomes (Mirzoev and Kane 2017). Healthcare services in Aotearoa, New Zealand are generally based on a colonial, Western biomedical model that was often misaligned to whānau values and expectations. Misalignment occurred in language barriers both in spoken languages and medicalised languages, assumptions that families were sedentary when in fact many were highly mobile, and in some cases homeless, and in values around collectivism, ageism and gendered norms (Burgess 2016; Anderson et al. 2019; Trace 2022). Of particular note was a gap in age-appropriate services and resources for teenagers with ARF/RHD, and similarly, lack of transition for patients from paediatric to adult services. Racism was experienced by ARF/RHD patients and whānau at all levels: institutional, interpersonal and internalised (Anderson et al. 2019; Anderson and Spray 2020). Interpersonal racism was experienced through verbal and non-verbal encounters, and, unfortunately, some whānau internalised messaging around ARF, expressing it was a condition of poor, brown, people, therefore perpetuating stigma of the disease.

Primordial prevention of ARF and RHD

Primordial prevention of RHD is modification of the social determinants of health to reduce the risk of Strep A infection and subsequent progression to RHD (Baker et al. 2023). There are decades of high-quality research on the positive benefits on health of warm, dry and safe homes in Aotearoa, New Zealand (He Kāinga Oranga–Housing and Health 2022). More recently, researchers in NZ have conducted two high-quality case-control studies to confirm the social determinants and identify risk factors for both ARF and Strep A infections (Baker et al. 2022; Bennett et al. 2022). The ARF risk factor study included 124 cases and 372 closely matched controls. It found that ARF risk was strongly associated with household crowding, barriers to accessing primary health care, a high intake of sugar-sweetened beverages and a family history of ARF. Risk was also elevated following self-reported skin infection and sore throat (Baker et al. 2022). These findings reinforce the importance of health determinants, notably an adequate supply of affordable housing to reduce the need for crowding, and good access to primary healthcare. The link with sugar-sweetened beverages supports continuing efforts to improve childhood nutrition.

Findings from the case-control study of Strep A infections found that children who had Strep A skin infections in particular had a similar pattern of risk factors to those seen for ARF, with an association with living in a crowded home, a family history of ARF and poor access to primary health care (Bennett et al. 2022). Together with other research, these findings point to the need for a much stronger focus on treating skin infections as well as Strep A pharyngitis as an intervention to reduce ARF (Oliver et al. 2021a).

Understanding the role of colonisation and poor health outcomes for Māori: Colonisation both in historical and contemporary contexts has created and maintained health inequities in NZ through key mechanisms of white privilege and racism (Reid et al. 2019; Curtis et al. 2023). These mechanisms operate through all major determinants of health such as housing, education and health (Houkamau and Sibley 2015). The Waitangi Tribunal's Wai 2750 Kaupapa inquiry into Māori Housing Policy and Services

(addressing numerous housing-related claims) has outlined the impact of years of insufficient responses to Māori housing issues that have had an intergenerational impact on Māori communities. These impacts continue to be felt today (Waitangi Tribunal-Te Rōpū Whakamana i te Tiriti o Waitangi 2020). The Tribunal in its Stage One report on homelessness found that:

> the Crown breached the treaty by its failure to adequately consult Māori over its definition of homelessness in 2009. Then, over the following seven years, the Crown did practically nothing to address Māori homelessness. It developed a Māori housing strategy that it did not implement, allowed the relative provision of social housing (on which Māori heavily rely) to decrease, and toughened access to the social housing register. All the while, problems of housing affordability were worsening.

There is a need to urgently scale up iwi- and Māori-led housing initiatives, which are already in progress (as foreseen in MAIHI Ka Ora–the National Māori Housing strategy) (Te Tūāpapa Kura Kāinga–Ministry of Housing and Urban Development 2023). Although the Whai Kāinga Whai Oranga funding pool of $731 m is the biggest investment in Māori housing and infrastructure in decades, this remains inadequate in the face of the need and the decades of neglect and requires long-term cross-party political commitment and scale-up. In addition to addressing housing, there is an urgent call to implement anti-racism and decolonising interventions in NZ, largely based around ensuring Indigenous rights are upheld and maintained across all levels and sectors of society (Came et al. 2021).

Primary prevention: sore throat management programme

In New Zealand, disease control in the past two decades has largely focused on primary prevention of ARF. Lennon's landmark primary prevention study involving 53 schools in South Auckland (Lennon et al. 2009) was begun in the late 1990s. The intervention was a school-based sore throat clinic program with free nurse-observed oral penicillin treatment of Strep A pharyngitis, and the control group received routine general practice care. Those in the intervention group showed a non-significant 28% reduction (26 cases, ARF rate 59/100,000 compared to 33 cases, ARF rate 77/100,000 $P = 0.27$).

Following the Māori party's co-leader Tariana Turia's advocacy for funding for ARF, the NZ Rheumatic Fever Prevention Programme (RFPP) (Te Whatu Ora 2023a) rolled out in 2012. The RFPP included several components. The largest component was a school-based sore throat service, aiming to prevent ARF through timely detection and treatment of Strep A pharyngitis. This service was delivered to high-risk children attending primary schools in areas of relative socioeconomic deprivation. The RFPP resulted in a 46% reduction in ARF in schools in South Auckland (Counties Manukau) but was less effective in schools in the other nine districts where it was operating (Jack et al. 2018) and did not reach the Ministry of Health's target of a two-thirds reduction in ARF rates. Some regional approaches continue to be successful (Malcolm et al. 2013; Anderson et al. 2016) but delivery and intensity of programme models varied considerably across regions, with a mix of rural/urban settings.

Effect of the NZRFPP on overall ARF rates in Aotearoa, NZ: First episodes of ARF for 2006–2022 are shown in Figure 1 (Te Whatu Ora 2023b). It should be noted that all those with suspected ARF are admitted to hospital (New Zealand Heart Foundation

Figure 1. First episode rheumatic fever hospitalisations, annual rate per 100,000, New Zealand 2006–2022. Source: Service Analysis and Modelling Evidence, Research and Analytics, Manatū Hauora. ICD codes used include: ICD-10-AM diagnosis code s: I00, I01, I02 (Acute rheumatic fever); ICD 9 CM-A diagnosis codes: 390, 3 91, 392 (Acute rheumatic fever); ICD-10-AM diagnosis codes: I05-I09 (Chronic rheumatic heart disease) and ICD 9 CM-A diagnosis codes: 393–398 (Chronic rheumatic heart disease).

2014). Following introduction of the RFPP in 2012, the incidence of ARF declined in 2014–2015, followed by an increase in 2016–2017. Introduction of the RFPP likely contributed to this initial decline.

Figure 2 shows ARF trends across time by ethnicity (Te Whatu Ora 2023b). Pacifica rates started to rise again in 2016, but from 2020, coinciding with the start of the Covid-19 pandemic and the introduction of strong pandemic control measures, rates again fell. Currently (2023–2024) Pacifica rates are rising. There has been a slow downward trend in rates for Māori from 2013, coinciding with the start of the RFPP, and Māori rates did not change during the Covid-19 pandemic period.

The RFPP has been very effective at raising the health literacy of the at-risk population: namely, the association of sore throats and ARF; the importance of seeking medical help for sore throats historically had low health literacy (Ministry of Health – Manatū Hauora 2011) rising to 70%, (Gurney et al. 2017) and 80%–90% in the Baker's risk factor study (Baker et al. 2022). However, Anderson and Spray have shown there were cultural deficiencies, including racism and ARF stigma, arising from the MOH health literacy messaging. They strongly argue that attending to how families experience public health messaging in the context of their daily lives may guide a more critical and culturally safe health promotion that looks beyond awareness and behaviour and towards equity (Anderson and Spray 2020). Tu'akoi and colleagues recommend co-designing interventions with affected communities could better ensure that future strategies are better targeted without contributing to further stigma (Tu'akoi et al. 2023).

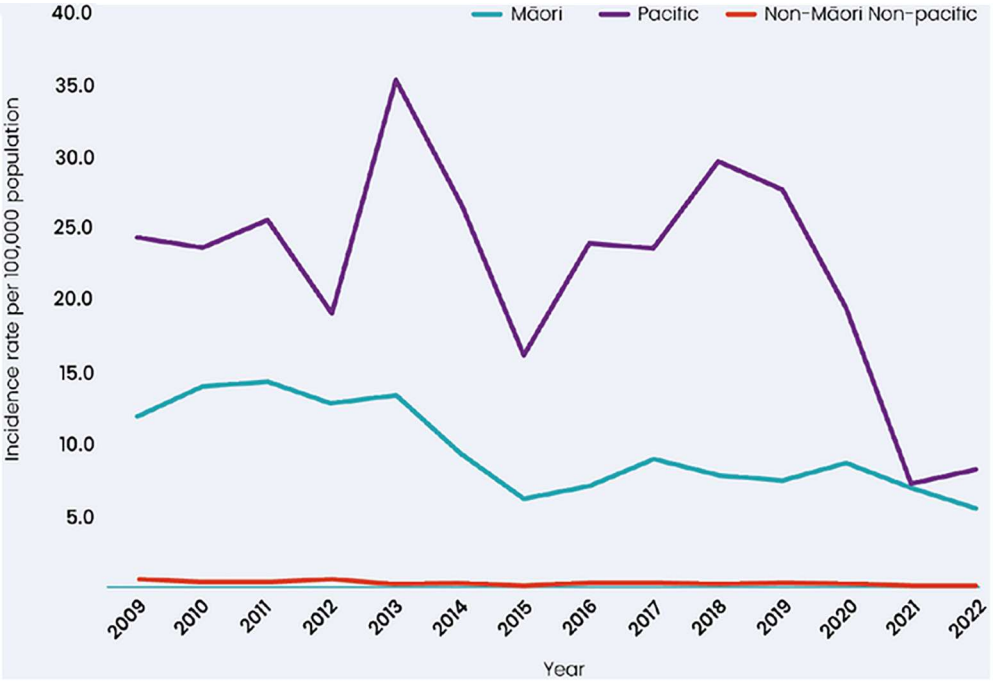

Figure 2. First episode rheumatic fever hospitalisations, annual rate per 100,000, by ethnic group, New Zealand, 2009/10-2021/22. Source: Service Analysis and Modelling Evidence, Research and Analytics, Manatū Hauora. ICD codes used include: ICD-10-AM diagnosis code s: I00, I01, I02 (Acute rheumatic fever); ICD 9 CM-A diagnosis codes: 390, 3 91, 392 (Acute rheumatic fever); ICD-10-AM diagnosis codes: I05-I09 (Chronic rheumatic heart disease) and ICD 9 CM-A diagnosis codes: 393–398 (Chronic rheumatic heart disease).

The ultimate goal of primary prevention globally is to develop an effective Strep A vaccine. In the interim, primary prevention will continue to be based on prompt treatment of Strep A throat and skin infections, delivered through a culturally appropriate framework.

Primary prevention: vaccine research and the international vaccine consortium

Efforts to develop an effective vaccine against Strep A stretch back decades (Walkinshaw et al. 2023). However, multiple barriers have impeded progress. These range from scientific and technical through to regulatory and commercial. Strain diversity (over 200 *emm*-types) poses coverage challenges for M-type specific vaccines, though this could potentially be circumvented if candidates based on highly conserved Strep A antigens show efficacy in clinical trials (Lacey et al. 2024). A preclinical candidate based on Strep A T-antigens (TeeVax) is being developed in NZ and may also provide adequate coverage if protection can be demonstrated in humans (Loh et al. 2021). Other challenges include the additional safety and regulatory requirements that will be required in early-stage clinical trials. This is due to the specific concern that a Strep A vaccine might trigger an autoimmune response similar to that seen in ARF, despite contemporary candidates being designed to avoid antigens/epitopes implicated in ARF (Fulurija et al. 2023).

Moreover, considerable large-scale investment will be required for development of a vaccine through to licensure.

These challenges were recognised by the Governments of NZ and Australia approximately 10 years ago and led to a co-funded trans-Tasman initiative tasked with developing tools required for Strep A vaccine development called CANVAS (**C**oalition to **A**dvance **N**ew **V**accines for Group **A** **S**treptococcus, 2014–2018) (Moreland et al. 2014; Schodel et al. 2017). The years since have seen continued advocacy and revitalisation of the field. This includes the need to prioritise a Strep A vaccine being recommended at the 71st World Health Assembly in 2018 (WHO 2018) and the formation of the **S**trep **A** **V**accine Global **C**onsortium (SAVAC), which aims to action the vaccine development roadmap formulated by the WHO (Walkinshaw et al. 2023). There has also been further investment from NZ and Australian governments resulting in the formation of ASAVI (**A**ustralian **S**trep **A** **V**accine **I**nitiative) and the NZ-based initiative named *Rapua te mea ngaro ka tau* (Seeking that which is hidden), with both aimed at accelerating vaccine development for the region. In NZ the focus is on enhanced surveillance, building laboratory capacity and clinical trial readiness. Qualitative data collection and critical Indigenous approaches are woven into all of the research phases of *Rapua te mea ngaro ka tau* to ensure responsive and equitable outcomes (University of Auckland–Waipapa Taumata Rau 2022).

Though the pipeline for Strep A candidates is comparably sparse and challenges remain, the renewed advocacy and investment in NZ, Australia and globally should accelerate all aspects of the vaccine pathway, making pivotal efficacy trials for the primary indications of Strep A pharyngitis and skin infections a reality before 2030.

Secondary prevention: BPG prophylaxis

For 70 years intramuscular benzathine penicillin G (BPG) has been used as secondary prophylaxis for ARF/RHD to prevent repeated Strep A infections that may worsen disease (Carapetis et al. 2016; Te Whatu Ora 2023b). In NZ, guidelines recommend patients with ARF have a minimum 10 years of secondary prophylaxis given as four-weekly BPG intramuscular (IM) injections (New Zealand Heart Foundation 2014). NZ has a strong track record of successful BPG delivery through community nursing services with high adherence and low recurrence rates in children (Newman et al. 1984; Spinetto et al. 2011). However, ARF recurrences are more common in young adults (Dennison et al. 2020). Globally, many RHD programmes struggle with secondary prevention delivery due to the pain of the injection and the frequency of delivery (Wilson 2013; Dougherty et al. 2018). Recently there have been new research developments with a Phase I trial showing that delivering high-dose BPG via subcutaneous infusion was safe, tolerable and suitable for up to three-monthly dosing intervals (Kado et al. 2020; Enkel et al. 2023). Following this, a NZ-based Phase II trial has shown that children and young adults currently receiving secondary prophylaxis for ARF preferred high-dose **S**ub**c**utaneous **I**nfusion of **P**enicillin (SCIP) over their usual IM BPG regimen, reporting less pain and a preference for the longer time gap (up to 70 days versus 28 days) between treatments (Bennett J, personal communication). After much advocacy for a National Register (Bennett et al. 2021a), this has been funded in 2022 (Te Whatu Ora 2023b) and will be known as the National Rheumatic Fever Care Coordination System.

Tertiary RHD

Over time, severe RHD leads to the complications of ventricular dysfunction due to chronic left ventricular dilatation, congestive heart failure, pulmonary hypertension, atrial fibrillation, stroke and premature mortality. Access to health systems including cardiac surgery influences RHD outcomes. In rural Ethiopia, the mean age of death for severe RHD was 22 years (Gunther et al. 2006), in Fiji less than 40 years (Parks et al. 2015) and in New Zealand 55 years (Milne et al. 2012; Tilton et al. 2022).

The detailed medical and surgical management of RHD is beyond the scope of this review.

In brief, the principles of management of RHD are described in the respective NZ and Australian RF/RHD guidelines (New Zealand Heart Foundation 2014; RHDAustralia (ARF/RHD writing group) 2020). International guidelines provide extensive guidance on the medical management of chronic heart failure, the main cause of death in RHD (Ponikowski et al. 2016; Yancy et al. 2017).

Evidence-based management for severe valvular heart disease in adults including thresholds for cardiac surgery and catheter interventions are updated every few years by the American Heart Association/American College of Cardiology guidelines (Otto et al. 2021) and European Society of Cardiology guidelines (Vahanian et al. 2022).

There is limited evidence-based data for threshold for cardiac surgery in children, with significant contributions from Green Lane and Starship Hospital cohorts (Gentles et al. 2001; Anderson et al. 2008; Remenyi et al. 2013a; Gentles et al. 2015). Repairs of the mitral valve are strived for (Finucane and Wilson 2013), as the quality of life is better, and outcomes are better than replacement in children. However, many will need a later valve replacement and lifelong need for anticoagulation. Unfortunately, the reality for severe disease in many low- and middle-income countries (LMIC), especially in the African continent and parts of Asia is that there is there is no prospect of cardiac surgery (Zilla et al. 2018).

Immunology and immunotherapy of acute rheumatic fever

Immunology: The pathogenesis of ARF involves complex immune dysregulation following Strep A infection, culminating in autoantibodies and self-reactive T cells targeting cardiac and other self-tissues (Carapetis et al. 2016). However, the underlying process resulting in this immune dysregulation, and in particular the mechanisms resulting in progression of rheumatic carditis to RHD are poorly understood. The prevailing hypotheses propose that antibodies initially developed in response to Strep A infection cross-react with cardiac tissue, increasing adhesion molecule expression in the heart (Carapetis et al. 2016). This, in combination with proinflammatory cytokines and chemokines, likely allows immune cell infiltration of cardiac tissue (Galvin et al. 2000; Roberts et al. 2001; Faé et al. 2013). Auto-reactive T cells are thought to perpetrate inflammatory damage within the heart that likely contributes to the fibrotic scarring and the progressive destruction of valve tissue (Ellis et al. 2005). This tissue damage is particularly severe in left-sided heart valves, which experience the highest pressure gradients and have limited ability to repair under chronic loading conditions (Karthikeyan et al. 2020; Okello et al. 2019).

Current concepts of the immunology of ARF revealed by contemporary technology: New insights of the immunology of ARF are in progress using contemporary tools and technology, particularly via studies conducted in NZ and Australia. There is a search for a new diagnostic test for ARF using these immunological assays combined with other biomarkers (Ralph et al. 2021).

Previous Strep A exposures have been mapped by quantifying serum antibody specificities with M-protein peptide arrays (Lorenz et al. 2021). This NZ-based study showed ARF cases had serologically confirmed reactivities to significantly more Strep A M-types compared to matched healthy controls and suggests that immunological 'priming' may occur whereby repeated Strep A infections result in the breakdown of tolerance and the development of ARF. Antibody responses in ARF have also been compared with precursor Strep A positive pharyngitis and skin infections using a custom 8-plex bead-based assay developed in NZ (Whitcombe et al. 2022). Here, increased breadth (more antigen-specific reactivities per person) and magnitude (higher average antibody titers to every antigen measured) was observed in ARF compared to precursor infections. This suggests increased immune activation in response to Strep A in ARF, possibly resulting from multiple priming events.

Autoantibody repertoires in ARF have been mapped with high-content protein microarrays encompassing thousands of human proteins (McGregor et al. 2021). A global increase in reactivity to auto-antigens (the targets of autoantibodies) was observed in ARF cases compared to controls, and disease pathway analysis identified immune pathways associated with arthritic and myocardial disease, supporting the relevance of identified antigen targets. However, autoantibody profiles were also found to be heterogenous between cases, and many antigen reactivities were to intracellular proteins. This suggests that epitope spreading may be involved in ARF pathogenesis, whereby inflammatory tissue damage results in presentation of additional auto-antigens and contributes to disease symptoms.

The relationship between immunoglobulin and the complement system has been investigated using bead-based assays and 'systems immunology' data analysis approaches (Chung et al. 2020). Complement factors and immunoglobulin isotypes were generally elevated in highly inflammatory ARF, with IgG3 and C4 being both significantly elevated and above clinical reference ranges. While this may suggest the involvement of the classical pathway of complement activation, another possibility is proinflammatory cytokines upregulating complement as part of acute phase reactant stimulation. A series of studies internationally have also shown proinflammatory cytokines are elevated in RHD, including IL-6, TNFα and IFNγ (Diamantino Soares et al. 2019; Tormin et al. 2021; Neves et al. 2021). The importance of cytokines in driving autoimmune disease in general provides the potential of therapeutic options for the blockade of cytokine signaling. Pre-existing therapies such as IL-6 blockade (e.g. tocilizumab) could be explored for use in the context of ARF and RHD (Middleton et al. 2022).

The role of cellular immunity has been investigated by applying RNAseq and multiplex cytokine assays to *in vitro* stimulation assays of PBMC from patients with ARF and healthy controls recruited in the Northern Territory of Australia (Kim et al. 2018). ARF exhibited T cell skewing toward a Th1 phenotype following *in vitro* stimulation of PBMC with heat-killed Strep A, along with increased TNFα, IL-1β, and GM-CSF secretion. This dysregulated cytokine axis was corrected following the *in vitro* addition of

Hydroxychloroquine (HCQ), resulting in reduced expansion of T cells producing GM-CSF and IFNγ. This finding has led to the current trials of HCQ as a treatment for ARF in NZ (Wilson et al. 2020).

Taken together, these studies have identified important features of the immune response to the infectious events preceding ARF and the immunological dysregulation characterising the disease. They suggest that common inflammatory mechanisms drive disease progression, and that these may be amenable to targeting by immune modulating therapy. Further research seeking to refine these therapeutic targets and validate the suitability of new biological therapies to prevent progression to chronic disease are warranted.

Immunomodulation treatment for ARF

Historical: NSAIDs are effective symptomatic treatments for the painful arthralgia and arthritis of ARF (Carapetis et al. 2005; New Zealand Heart Foundation 2014). However, no immunomodulatory treatment has been shown to alter cardiac outcomes for patients with ARF (Cilliers et al. 2012; Cilliers et al. 2015). In 1954, Illingworth et al reviewed 170 articles and found no influence of aspirin on carditis (Illingworth et al. 1954). A meta-analysis of five RCTs of corticosteroid treatment (Albert et al. 1995) showed no difference in clinical cardiac outcomes (in the era prior to echocardiography) with one-year follow up. There was minor variation in outcome for smaller studies but no evidence of limitation of valve lesions, although a response of 10% could have been missed. The meticulous RCT of the UK–USA working group (Rheumatic Fever Working Party 1965) was the largest RCT and dominates the meta-analysis. Despite this, corticosteroids are often prescribed in many centres in the world, most likely as the inflammatory markers of ARF quickly subside. We suggest, however, that there is still a place to restudy the effects of corticosteroids in ARF with echocardiographic endpoints and in conjunction with contemporary immunological assays. Combination interventions with corticosteroids and other immune-modulators could also be considered in future clinical trials.

The severity of carditis (more specifically valvulitis) at the resolution of the acute phase of ARF largely determines the severity of chronic RHD. The last RCT for treatment of carditis was performed in New Zealand in the 1990s using intravenous immunoglobulin (Voss et al. 2001) and showed no significant benefit in the evolution of RHD. Again, a small treatment effect could have been missed. Since the IVIG study, there have been no new medical interventions trialled in ARF, in part due to a lack of proposed candidate immunomodulators and in part due to lack of researchers globally.

Current immunomodulator trial of hydroxychloroquine in New Zealand: As noted above, in 2018 the Kim et al *ex vivo* study (Kim et al. 2018) suggested that HCQ may have potential in ARF. HCQ has been used for decades to treat autoimmune disorders such as systemic lupus erythematosis (Costedoat-Chalumeau et al. 2014; Ponticelli and Moroni 2017). It has also been used for over 60 years for the treatment and prevention of malaria (Shippey et al. 2018). HCQ is inexpensive, an important characteristic for treatments of ARF and RHD that persist in LMIC. Its safety profile is well established (Costedoat-Chalumeau et al. 2005).

In 2019 we used HCQ in two children with ARF and atypically prolonged inflammatory trajectories, a world first (Wilson et al. 2020). HCQ was given after nine weeks of

relapsing symptomatic pericarditis despite corticosteroid treatment in the first patient, and in the second after four months of progressively increasing valvulitis and rebound arthritis. In both patients, symptoms and inflammatory markers were controlled within two weeks, the pericarditis was controlled in the first patient, and the valvulitis stabilised in the second patient.

An international group of ARF and RHD researchers met in Cape Town, also in 2019, where possible ARF treatment trials were discussed in detail, chaired by Professor Liesl Zühlke. It was noted that large-scale multi-site RCT of HCQ versus corticosteroids would likely take years to complete.

The use of high dose HCQ in the Covid-19 pandemic had raised concerns about QTc interval prolongation and direct cardiac arrhythmias in adults (Roden et al. 2020; Shukla et al. 2020). We had recently studied QTc prolongation in ARF in a contemporary cohort of 197 children <15 years of age with ARF. The QTc mean (SD) was 445 msec (28), range 370–545 msec. Eighteen percent of the cohort had a QTc > 99th percentile for normal by age (Perelini et al. 2022). No cardiac arrhythmias were observed, supporting previous observations that QTc prolongation in ARF is almost always benign. There is a lack of detailed data of serial evolution of QTc in ARF but ventricular tachycardia has only been reported in two case reports, one in 1937 and one in 2001 (Karacan et al. 2010; Perelini et al. 2022). However, serial ECG monitoring of the QT interval is clearly recommended for any treatment such as HCQ, which can also prolong QTc, and in ARF where QTc can initially be prolonged.

In 2021 we commenced a HCQ treatment for ARF, aka 'HYDxARF', Universal trial number: U1111-1243-7009. This is a proof of a concept pilot trial examining safety, efficacy and tolerability of HCQ in ARF. Detailed cytokine and immune cell profiling will be undertaken pre- and post-HCQ to understand the immunomodulatory mode of action of HCQ in ARF *in vivo*.

HYDRxARF may also aid powering of a larger RCT. The study inclusions are participants with ARF with carditis, aged under 16 years. Those with ARF and no carditis were excluded. The dose regimen used is the standard anti-inflammatory regimen for children of 5–7 mg/kg once a day, maximum 400 mg; treatment duration four weeks for mild or moderate carditis, six weeks for severe carditis, HCQ was withheld if QTc exceeded Mayo clinic guidelines (Giudicessi et al. 2020).

The protocol included inpatient observation ≥ one week from enrolment for potential adverse effects and serial ECGs for QTc monitoring in the first week of treatment with HCQ. Outpatient adherence was checked with text/phone reminders to the whānau. Echocardiographic time points for severity of carditis: pre- and two weeks, six weeks and six months post-HCQ.

The early inflammatory course of ARF including the rate of fall of laboratory inflammatory markers (ESR and CRP) and control of arthritis was evaluated. A comparison of clinical data compared to a contemporary age and cardiac severity matched ARF cohort will be undertaken.

Immunological analysis will include spectral flow cytometry profiling of peripheral immune cell populations and the quantification of peripheral cytokines. This aims to elucidate the complex immune cell dynamics coordinated by cytokines and chemokines following a treatment course with HCQ. In addition, *in vitro* stimulation assays of immune cells with heat-killed Strep A following published protocols will allow characterisation of changes in cytokine release over the course of treatment and resolution of inflammation (Kim et al. 2018).

Table 1. Principles for clinical trials of immuno-modulation in ARF.

1.	There is sufficient uncertainty and clinical equipoise to support randomisation into a clinical trial of a potential immuno-modulator
2.	The need for multiple international sites, in order to recruit adequate numbers of patients with inflammatory phase ARF
3.	Trial design: whether frequentist or adaptive design is best placed to address research questions in light of disease features
4.	Appropriate clinical and laboratory endpoints, acknowledging the natural history of carditis. The natural history of ARF, in the absence of recurrent episodes of RF, is for disease improvement in the majority of patients, need consideration for powering RCTs

Our immunomodulatory research group is multi-disciplinary and includes Māori and Pacific researchers, paediatricians, paediatric infectious diseases, paediatric and adult cardiology, rheumatology and immunology scientists.

Future: The immune-pathogenesis studies to date suggest that common immunoinflammatory mechanisms drive disease progression that may be amenable to targeting by immune modulating drugs. There is a clear need for well-designed RCTs to identify effective treatments, including new biological therapies, for ARF that minimise long-term cardiac damage. Considerations for such future trials are shown in the Table 1.

It should be noted that there are several hurdles in developing evidence for effective immuno-modulation in ARF. Firstly, the time from the antigen (symptomatic or asymptomatic Strep A throat/skin infection), to the commencement of treatment. There is characteristically a one-to-three-week interval from the Strep A infection to the onset of the inflammatory response and ARF symptoms. Presentation to health services may take time, and days may be required to confirm the diagnosis. In the IVIG RCT, the average duration of symptoms before IVIG was nine days (Voss et al. 2001). These delays allow the immune-pathogenesis to advance, which might negate the potential benefit of immunosuppression treatment.

Secondly, powering for RCTs is also problematic, as the natural history of mild and moderate carditis is to improve in the following 6 to 12 months (Wilson et al. 1997). In our IVIG study using echocardiographic assessment, 27% of patients given placebo showed a return to normal, and similarly, 35% of valves with mitral or aortic regurgitation returned to normal (Voss et al. 2001).

Thirdly, in LMIC, most patients present with established RHD rather than ARF (Zhang et al. 2015) with less recognition of ARF. However, this has been partly addressed in a prospective study by Okello and colleagues in Uganda (Okello et al. 2021). This population-based study estimated the incidence of acute rheumatic fever in sub-Saharan Africa by setting up community clinics. Healthcare workers were encouraged to refer children with a history of fever and any joint complaints for a full diagnostic work up for ARF. Significant rates of ARF were found, and the data dispels the long-held hypothesis that ARF did not exist in sub-Saharan Africa. The findings compel investment in improving prevention, recognition and diagnosis of acute rheumatic fever in regions where RHD is endemic but ARF infrequently recognised.

Echocardiographic case detection as a means of disease control

The Rationale for screening for RHD: In NZ between 38% (Registry data) (Tilton et al. 2022) and 80% (ICD code data) (Oliver et al. 2021b) of those presenting with chronic RHD have not had a previous recognised episode of ARF. In many resource-limited settings, RHD is frequently diagnosed at a late stage. In Uganda, 85% of newly diagnosed patients with RHD presented with severe valvular involvement and cardiovascular complications (Zhang et al. 2015). Screening aims to identify RHD before an individual develops clinical disease.

In earlier decades, the WHO endorsed auscultation for screening for RHD. However, auscultation has been shown to be inaccurate with low sensitivity (Carapetis et al. 2008). The field of echocardiographic screening has emerged since the landmark study by Marijon et al from Cambodia and Mozambique in 2007 (Marijon et al. 2007), where echocardiography revealed a tenfold higher detection of RHD than auscultation. This mismatch between auscultation and echocardiographic findings was confirmed in subsequent studies (Roberts et al. 2013). Since 2007, echocardiographic screening has revealed a large burden of undiagnosed RHD in many LMIC, broadened our understanding of the prevalence of RHD within endemic communities and provided advocacy for international global attention on RHD. Until recently, echo screening has been in the research domain, rather than proven as a means of disease control.

There has been a body of research from New Zealand building the evidence for portable echocardiography as a suitable test for screening for RHD. An initial prevalence study in South Auckland was undertaken in primary schools for 1142 students aged 10–13 years (Webb et al. 2011). The prevalence of any RHD ('definite, probable and possible') was 5.2% using non-standardised criteria. Another 2.6% had non-rheumatic cardiac abnormalities, some with minor congenital rather than rheumatic mitral valve anomalies. Echocardiographic normative data for valve thickness had surprisingly not been established for children. A standardised method for mitral and aortic valve measurement in a cohort of 288 children was shown to be objective and reproducible (Webb et al. 2017). Minor physiological valvular regurgitation, a feature of normal valves, can be separated from pathological degrees of mild valvular regurgitation. Building from our experience in ARF and valve regurgitation in children (Wilson and Neutze 1995; Wilson 2008; Wilson et al. 2013), we studied the prevalence of valvular regurgitation in a low-RF population using portable echocardiography. Physiologic mitral regurgitation (MR) was present in 14.9% of 396 students aged 10–12 years, and 0.5% had pathological MR which met the criteria of borderline RHD (Webb et al. 2015). This was similar to that found in two other studies in low-RF populations, with 0.5% found in Australia (Roberts et al. 2014) and 0.8% in the United States (Clark et al. 2015).

In the first years of screening from 2007, cardiologists were using a variety of diagnostic criteria for RHD. There was a need for standardisation both for epidemiological data and individual case management. An international group of investigators was formed and led from New Zealand, and standardisation of the minimal criteria for RHD known as the WHF criteria was achieved (Remenyi et al. 2013b). This immediately became the gold standard for the echocardiographic diagnosis of mild RHD for the following decade and has been widely cited. Good inter-observer agreement has been found using the WHF criteria internationally (Remenyi et al. 2019) and locally (Culliford-

Semmens et al. 2019). A second iteration of the WHF criteria, led by an expanded global group of RHD researchers, was published in 2023 (Rwebembera et al. 2023).

Screening has also been undertaken in other New Zealand regions: Tairawhiti (Cramp et al. 2012); Porirua (Perelini et al. 2015); Bay of Plenty (Malcolm et al. 2013); and Northland (Tuck R unpublished). Family acceptability was studied as part of the Porirua programme with the families of 34 children with abnormal scan results and a sample of 80 children with normal scan results surveyed within four months of screening. Positive results were seen in all survey questions in both normal and abnormal scan groups. All families were supportive of an ongoing screening programme. However, for children with abnormal results, 62% of their parents reported that they would treat their child differently.

The potential harms of screening in the New Zealand setting were studied in more detail led by Public Health researchers from the University of Otago (Gurney et al. 2016). A total of 91 parents/caregivers of children diagnosed with RHD, 'abnormal' cases, were interviewed along with at least two matched 'normal' controls. It was found that there were diminished physical activity habits in 20% of those with an abnormal result that persisted longer than 6 months. Twenty-five percent of the parents were still concerned about the abnormal result months to years later. These two studies, and other international literature (Wark et al. 2013), point out the need for adequate infrastructure support beyond the initial screening. Mild and moderate RHD does not cause haemodynamic limitations, so parents and the wider whānau need reassurance that the child can and should participate in normal exercise including full sports participation.

Most screening studies have been undertaken in school children, as they have the most to gain in terms of prevention of RHD. As expected, higher rates of RHD are found in adults than children in Aotearoa, New Zealand (Webb 2019; Webb et al. 2023) but screening in adults may find more advanced disease. Targeted screening for RHD in pregnancy (Otto et al. 2011; Nascimento et al. 2021) can be logical for women in high-prevalence LMIC countries where undiagnosed RHD, especially mitral stenosis, carries the risk of maternal mortality (Beaton et al. 2018; Rokovunisei et al. 2023).

In the NZ setting it has been shown that adherence to secondary prophylaxis with benzathine penicillin (BPG) for those detected with RHD is as good as that following ARF (Culliford-Semmens et al. 2017). The small (2%–3%) but importantly increased familial risk of RHD (whether environmental or genetic or both) was found in Aotearoa, New Zealand (Culliford-Semmens et al. 2021) and confirmed in Uganda (Aliku et al. 2016). This familial risk was also found in the ARF risk factor study in New Zealand (Baker et al. 2022).

Initially, there was no evidence from screening programmes that those on penicillin had better outcomes than those not receiving penicillin (Karthikeyan 2016), likely due to non-matched groups with a bias by researchers to placing those with more advanced RHD on BPG. This equipoise meant that an RCT was ethical and led to the 'GOAL' study, an RCT from Uganda (Beaton et al. 2022). In the GOAL study, 799 children with mild RHD were randomised to BPG or not. After 2 years, 8.3% of the non-treated group showed RHD progression compared to 1.3% of those receiving BPG. Thus, the GOAL study provides the evidence that penicillin is effective in preventing disease progression for those with echocardiographic mild RHD. It also suggests that

up-scaled echocardiographic screening has the potential to be a significant element of RHD disease control globally.

Moreover, after 15 years of research, echocardiographic screening now meets the broad brushstrokes for the criteria for a reasonable screening test: the condition is an important health issue, there is a recognisable latent or asymptomatic phase, the natural history is understood, there is a suitable test and there is an accepted treatment that changes outcomes (National Advisory Committee on Health and Disability 2003). However, it is not known if there is the logistical workforce to develop a sustained programme of RHD screening in Aotearoa, particularly the sonographer and cardiology reporting workforce. In their RF and RHD roadmap 2023–2028, Te Whatu Ora announced funding for a demonstration pilot of RHD echo screening for tamariki and rangatahi in high-RHD prevalence regions. The pilot, using an implementation science approach, would assess community buy-in, workforce logistics and models (e.g. school-based and mobile bus) required for a national screening programme (https://www.tewhatuora.govt.nz/publications/rheumatic-fever-roadmap-2023–2028) (Te Whatu Ora 2023b).

RHD echocardiography screening is performed in the community, not in hospital. Technological advances in ultrasound, enabling portable and hand-held echocardiography, allow point-of-care ultrasound (POCUS) (Abrokwa et al. 2022). Globally, task shifting is a strategy endorsed by the WHO to improve efficiency in healthcare systems with shortages in skilled healthcare workers (World Health Organisation 2007). The concept, when applied to RHD echocardiographic screening, is for the initial screening echocardiography to be performed by 'briefly trained' health workers who have undergone shorter, focused training programs. This model has been adapted for RHD screening in LMIC to address the shortage of skilled RHD echo screening staff. In effect this is task sharing rather than complete task shifting, as expert interpretation of the images is still required. Task sharing in RHD benefits communities through upskilling local healthcare and community workers, thus creating employment opportunities, and provides equitable access to care with provision of screening in culturally appropriate ways (Francis et al. 2023). Such community-driven initiatives also increase awareness of rheumatic fever, improving health literacy, and engenders local leadership essential to improving outcomes (Carapetis and Brown 2020; Mitchell et al. 2021).

Several studies between 2013 and 2023 have reported on RHD screening performed by non-experts in approximately 18,850 children and young adults (Colquhoun et al. 2013; Mirabel et al. 2015; Beaton et al. 2016; Engelman et al. 2016; Nascimento et al. 2016; Ploutz et al. 2016; Diamantino et al. 2018; Schwaninger et al. 2018; Francis et al. 2021; Voleti et al. 2021; Elazrag et al. 2023; Francis et al. 2023). Most include a focused training period of didactic learning and direct supervision of training scans by expert tutors. Freely accessible online training modules developed for RHD echocardiography screening training have been utilised to shorten the overall face-to-face instruction period from several weeks to as short as 11 hours (Voleti et al. 2021; Engelman et al. 2023). Abbreviated screening protocols reduce the number of echocardiography windows non-experts are required to learn, with the 'SPLASH' protocol requiring as few as six images in the PLAX view (Remenyi et al. 2020). Most studies have used hand-held devices. The diagnostic accuracy ($n = 9$) has been reported with sensitivity ranging between 54% and 95% (most reporting sensitivity over 78.9%) and specificity 65%–95% (most reporting specificity above 79%).

The task-sharing model still requires a two-stage approach to RHD screening. The stage 1 screening echocardiogram is performed by non-expert screeners. The stage 2 comprehensive echocardiogram and review can occur immediately, or after an interval, depending upon the setting and availability of expert (usually cardiology) input. The final diagnosis can be made utilising the screening images if diagnostic, or after the comprehensive echocardiogram based on the most recent WHF 2023 criteria (Remenyi et al. 2020; Rwebembera et al. 2023). It is likely that artificial intelligence will have a role in reducing the time for analysis of images, both for the screening echocardiogram and the comprehensive analysis (Peck et al. 2023).

Each region or country should improve their models of delivery to make it truly accessible as a screening tool at the community level, beyond research projects, in a way that can be built into routine service delivery, through task-sharing approaches. This approach is being developed in primary schools in Fiji Islands as part of the school health nurse programme (Malo et al. 2023). Francis and colleagues articulate these concepts well in their discussion of a recent study (Francis et al. 2023). Health system issues within New Zealand, such as long waiting lists for echocardiography, a shortage in, and inequitable distribution of the sonographer workforce, potentially preclude RHD screening (Buckley et al. 2015). The 'Te Maatai Manawa a Whaanau: Family heart screening study' is a nurse-led novel pilot study of RHD screening for South Auckland children and young adults at high risk for RHD. The study has been co-designed with the community and aims to enrol siblings of children diagnosed with rheumatic fever to test whether a non-expert model can increase the equity in access and acceptability of RHD screening in NZ under a culturally safe model of delivery (Dennison et al. 2023).

Conclusions

ARF and RHD control in Aotearoa, NZ should maximise recent research findings. Efficacious immunomodulators to suppress the cardiac effects of ARF would be a game changer to reduce the burden of RHD. There is a need to move the echocardiographic detection of RHD from the research domain to translational science through a Māori and Pacific framework. To improve the unacceptable health system experiences for those living with ARF and RHD and redevelop culturally responsive services, the health sector needs strong advocacy and implementation of cultural safety and decolonisation approaches. Moreover, new initiatives should be led, or at least co-led, by those with lived experience who hold unique expertise in their health and cultural contexts (Anderson et al. 2020; Wyber et al. 2021b).

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References

Abrokwa SK, Ruby LC, Heuvelings CC, Bélard S. 2022. Task shifting for point of care ultrasound in primary healthcare in low- and middle-income countries-a systematic review. EClinicalMedicine. 45:101333. doi:10.1016/j.eclinm.2022.101333.

Albert DA, Harel L, Karrison T. 1995. The treatment of rheumatic carditis: a review and meta-analysis. Medicine. 74(1):1–12. doi:10.1097/00005792-199501000-00001.

Aliku T, Sable C, Scheel A, Tompsett A, Lwabi P, Okello E, McCarter R, Summar M, Beaton A. 2016. Targeted echocardiographic screening for latent rheumatic heart disease in Northern Uganda: evaluating familial risk following identification of an index case. PLoS Negl Trop Dis. 10(6):e0004727. doi:10.1371/journal.pntd.0004727.

Anderson A, Brown R, Wheeler J, Jansen RM. 2020. Pacific Fono: a community-based initiative to improve rheumatic fever service delivery for Pacific peoples in South Auckland. J Prim Health Care. 12(4):384–390. doi:10.1071/HC20022.

Anderson A, Peat B, Ryland J, Ofanoa M, Burgess H, Malungahu G, Wade J, Spray J, Leversha A. 2019. Mismatches between health service delivery and community expectations in the provision of secondary prophylaxis for rheumatic fever in New Zealand. Aust N Z J Public Health. 43(3):294–299. doi:10.1111/1753-6405.12890.

Anderson A, Spray J. 2020. Beyond awareness: towards a critically conscious health promotion for rheumatic fever in Aotearoa, New Zealand. Social Science & Medicine. 247:112798. doi:10.1016/j.socscimed.2020.112798.

Anderson P, King J, Moss M, Light P, McKee T, Farrell E, Stewart J, Lennon D. 2016. Nurse-led school-based clinics for rheumatic fever prevention and skin infection management: evaluation of Mana Kidz programme in Counties Manukau. N Z Med J. 129(1428):37–46.

Anderson Y, Wilson N, Nicholson R, Finucane K. 2008. Fulminant mitral regurgitation due to ruptured chordae tendinae in acute rheumatic fever. Journal of Paediatrics & Child Health. 44(3):134–137. doi:10.1111/j.1440-1754.2007.01214.x.

Baker MG, Gurney J, Moreland NJ, Bennett J, Oliver J, Williamson DA, Pierse N, Wilson N, Merriman TR, Percival T, et al. 2022. Risk factors for acute rheumatic fever: a case-control study. Lancet Reg Health West Pac. 26:100508. doi:10.1016/j.lanwpc.2022.100508.

Baker MG, Masterson MY, Shung-King M, Beaton A, Bowen AC, Bansal GP, Carapetis JR. 2023. Research priorities for the primordial prevention of acute rheumatic fever and rheumatic heart disease by modifying the social determinants of health. BMJ Glob Health. 8:e012467. doi:10.1136/bmjgh-2023-012467.

Beaton A, Nascimento BR, Diamantino AC, Pereira GT, Lopes EL, Miri CO, Bruno KK, Chequer G, Ferreira CG, Lafeta LC, et al. 2016. Efficacy of a standardized computer-based training curriculum to teach echocardiographic identification of rheumatic heart disease to nonexpert users. Am J Cardiol. 117(11):1783–1789. doi:10.1016/j.amjcard.2016.03.006.

Beaton A, Okello E, Rwebembera J, Grobler A, Engelman D, Alepere J, Canales L, Carapetis J, DeWyer A, Lwabi P, et al. 2022. Secondary antibiotic prophylaxis for latent rheumatic heart disease. N Engl J Med. 386(3):230–240. doi:10.1056/NEJMoa2102074.

Beaton A, Okello E, Scheel A, DeWyer A, Ssembatya R, Baaka O, Namisanvu H, Njeri A, Matovu A, Namagembe I, et al. 2018. Impact of heart disease on maternal, fetal and neonatal outcomes in a low-resource setting. Heart. 105(10):755–760. doi:10.1136/heartjnl-2018-313810.

Bennett J, Anderson A, Ofanoa M, Anderson P, Baker MG, Brown R, Devlin G, Eggleton K, Harwood M, Jansen RM, et al. 2021a. Acute rheumatic fever-a preventable, inequitable disease: a call for action. N Z Med J. 134(1535):93–95.

Bennett J, Moreland NJ, Zhang J, Crane J, Sika-Paotonu D, Carapetis J, Williamson DA, Baker MG. 2022. Risk factors for group A streptococcal pharyngitis and skin infections: a case control study. Lancet Reg Health West Pac. 26:100507. doi:10.1016/j.lanwpc.2022.100507.

Bennett J, Rentta N, Leung W, Anderson A, Oliver J, Wyber R, Harwod M, Webb R, Malcom J, Baker MG. 2021b. Structured review of primary interventions to reduce group A streptococcal infections, acute rheumatic fever and rheumatic heart disease. J Paediatr Child Health. 57(6):797–802. doi:10.1111/jpc.15514.

Buckley BA, Poppe K, Farnworth MJ, Whalley G. 2015. Regional differences in echocardiography provision in New Zealand–results from the 2013 SCANZ workforce survey. N Z Med J. 128 (1408):47–55.

Burgess H. 2016. Thesis: Māori whānau experiences of rheumatic fever: reflections of social and structural inequity [master's thesis]. Auckland: University of Auckland.

Came H, Baker M, McCreanor T. 2021. Addressing structural racism through constitutional transformation and decolonization: insights for the New Zealand health sector. J Bioeth Inq. 18 (1):59–70. doi:10.1007/s11673-020-10077-w.

Carapetis JR, Beaton A, Cunningham MW, Guilherme L, Karthikeyan G, Mayosi BM, Sable C, Steer A, Wilson N, Wyber R, et al. 2016. Acute rheumatic fever and rheumatic heart disease. Nature Reviews Disease Primers. 2:15084. doi:10.1038/nrdp.2015.84.

Carapetis JR, Brown A. 2020. Community leadership and empowerment are essential for eliminating rheumatic heart disease. Med J Aust. 213(3):116–117. doi:10.5694/mja2.50695.

Carapetis JR, Hardy M, Fakakovikaetau T, Taib R, Wilkinson L, Penny DJ, Steer AC. 2008. Evaluation of a screening protocol using auscultation and portable echocardiography to detect asymptomatic rheumatic heart disease in Tongan schoolchildren. Nat Clin Pract Cardiovasc Med. 5(7):411–417. doi:10.1038/ncpcardio1185.

Carapetis JR, McDonald M, Wilson NJ. 2005. Acute rheumatic fever. The Lancet. 366(9480):155. doi:10.1016/S0140-6736(05)66874-2.

Chung AW, Ho TK, Hanson-Manful P, Tritscheller S, Raynes JM, Whitcombe AL, Tay ML, McGregor R, Lorenz N, Oliver JR, et al. 2020. Systems immunology reveals a linked IgG3-C4 response in patients with acute rheumatic fever. Immunol Cell Biol. 98(1):12–21. doi:10.1111/imcb.12298.

Cilliers A, Adler AJ, Saloojee H. 2015. Anti-inflammatory treatment for carditis in acute rheumatic fever. Cochrane Database of Systematic Reviews. 5:CD003176.

Cilliers A, Manyemba J, Adler AJ, Saloojee H. 2012. Anti-inflammatory treatment for carditis in acute rheumatic fever. Cochrane Database of Systematic Reviews. 6:CD003176.

Clark BC, Krishnan A, McCarter R, Scheel J, Sable C, Beaton A. 2015. Using a low-risk population to estimate the specificity of the World Heart Federation criteria for the diagnosis of rheumatic heart disease. J Am Soc Echocardiogr. 29(3):253–258. doi:10.1016/j.echo.2015.11.013.

Colquhoun SM, Carapetis JR, Kado JH, Reeves BM, Remenyi B, May W, Wilson NJ, Steer AC. 2013. Pilot study of nurse-led rheumatic heart disease echocardiography screening in Fiji–a novel approach in a resource-poor setting. Cardiol Young. 23(4):546–552. doi:10.1017/S1047951112001321.

Costedoat-Chalumeau N, Amoura Z, Huong DL, Lechat P, Piette JC. 2005. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. Review of the literature. Autoimmun Rev. 4(2):111–115. doi:10.1016/j.autrev.2004.11.009.

Costedoat-Chalumeau N, Dunogue B, Morel N, Le Guern V, Guettrot-Imbert G. 2014. Hydroxychloroquine: a multifaceted treatment in lupus. Presse Medicale (Paris, France: 1983). 43(6 Pt 2):e167–e180. doi:10.1016/j.lpm.2014.03.007.

Cramp G, Stonehouse M, Webb R, Chaffey-Aupouri G, Wilson N. 2012. Undetected rheumatic heart disease revealed using portable echocardiography in a population of school students in Tairawhiti, New Zealand. N Z Med J. 125(1363):53–64.

Culliford-Semmens N, Nicholson R, Tilton E, Stirling J, Sidhu K, Webb R, Wilson N. 2019. The world heart federation criteria raise the threshold of diagnosis for mild rheumatic heart disease: three reviewers are better than one. Int J Cardiol. 291:112–118. doi:10.1016/j.ijcard.2019.02.058.

Culliford-Semmens N, Tilton E, Webb R, Lennon D, Paku B, Malcolm J, French S, Blair N, Wilson N. 2017. Adequate adherence to benzathine penicillin secondary prophylaxis following the diagnosis of rheumatic heart disease by echocardiographic screening. N Z Med J. 130(1457):50–57.

Culliford-Semmens N, Tilton E, Wilson N, Stirling J, Doughty R, Gentles T, Peat B, Dimalapang E, Webb R. 2021. Echocardiography for latent rheumatic heart disease in first degree relatives of children with acute rheumatic fever: implications for active case finding in family members. EClinicalMedicine. 37:100935. doi:10.1016/j.eclinm.2021.100935.

Curtis E, Jones R, Willing E, Anderson A, Paine SJ, Herbert S, Loring B, Dalgic G, Reid P. 2023. Indigenous adaptation of a model for understanding the determinants of ethnic health inequities. Discover Social Science and Health. 3(1):10. doi:10.1007/s44155-023-00040-6.

Dennison A, Anderson A, Brown R, Ikiua M, Philipson-Puna T, Chan Mow F, McCann L, Wilson N, Webb R. 2023. Te Mäatai Manawa a whanau: Family Health Screening Study. World Congress on Rheumatic Heart Disease. Abu Dhabi. 168.

Dennison A, Peat B, Wilson E, Leversha A, Wheeler M, Briggs S, Galloway Y, Ryland J, Wilson N. 2020. Rheumatic fever recurrences in New Zealand 2010–14. N Z Med J. 133(1516):47–57.

Diamantino A, Beaton A, Aliku T, Oliveira K, Oliveira C, Xavier L, Perlman L, Okello E, Nascimento B, Ribeiro ALP, et al. 2018. A focussed single-view hand-held echocardiography protocol for the detection of rheumatic heart disease. Cardiol Young. 28(1):108–117. doi:10.1017/S1047951117001676.

Diamantino Soares AC, Araújo Passos LS, Sable C, Beaton A, Ribeiro VT, Gollob KJ, Dutra WO, Nunes MCP. 2019. Circulating cytokines predict severity of rheumatic heart disease. Int J Cardiol. 289:107–109. doi:10.1016/j.ijcard.2019.04.063.

Dougherty S, Beaton A, Nascimento BR, Zuhlke LJ, Khorsandi M, Wilson N. 2018. Prevention and control of rheumatic heart disease: overcoming core challenges in resource-poor environments. Ann Pediatr Cardiol. 11(1):68–78. doi:10.4103/apc.APC_135_17.

Elazrag A, Altahir A, Abbas A, Hasabo EA, Ahmed H, Ali H, Abdelrazig I, Ahmed M, Almahal M, Siddig M, et al. 2023. Handheld echocardiographic screening for rheumatic heart disease by non-experts in rural South Kordofan, Sudan: supporting task shifting for control of a serious disease. Int J Cardiol. 377:99–103. doi:10.1016/j.ijcard.2023.01.024.

Ellis NM, Li Y, Hildebrand W, Fischetti VA, Cunningham MW. 2005. T cell mimicry and epitope specificity of cross-reactive T cell clones from rheumatic heart disease. J Immunol. 175(8):5448–5456. doi:10.4049/jimmunol.175.8.5448.

Engelman D, Kado JH, Remenyi B, Colquhoun SM, Carapetis JR, Donath S, Wilson NJ, Steer AC. 2016. Focused cardiac ultrasound screening for rheumatic heart disease by briefly trained health workers: a study of diagnostic accuracy. Lancet Glob Health. 4(6):e386–e394. doi:10.1016/S2214-109X(16)30065-1.

Engelman D, Watson C, Remenyi B, Steer A. 2023. Echocardiographic diagnosis of rheumatic heart disease: nurse training modules: WiREDInternational. Berkeley, California, USA: Wired International Health Education and Information; [accessed]. http://www.wiredhealthresources.net/EchoProject/index.html.

Enkel SL, Kado J, Hla TK, Salman S, Bennett J, Anderson A, Carapetis JR, Manning L. 2023. Qualitative assessment of healthy volunteer experience receiving subcutaneous infusions of high-dose benzathine penicillin G (SCIP) provides insights into design of late phase clinical studies. PLoS One. 18(4):e0285037. doi:10.1371/journal.pone.0285037.

Faé KC, Palacios SA, Nogueira LG, Oshiro SE, Demarchi LM, Bilate AM, Pomerantzeff PM, Brandão C, Thomaz PG, dos Reis M, et al. 2013. CXCL9/Mig mediates T cells recruitment to valvular tissue lesions of chronic rheumatic heart disease patients. Inflammation. 36(4):800–811. doi:10.1007/s10753-013-9606-2.

Finucane K, Wilson N. 2013. Priorities in cardiac surgery for rheumatic heart disease. Glob Heart. 8(3):213–220. doi:10.1016/j.gheart.2013.08.010.

Francis JR, Fairhurst H, Yan J, Fernandes Monteiro A, Lee AM, Maurays J, Kaethner A, Whalley GA, Hardefeldt H, Williamson J, et al. 2023. Abbreviated echocardiographic screening for rheumatic heart disease by non-experts with and without offsite expert review: a diagnostic accuracy study. J Am Soc Echocardiogr. 36(7):733–745. doi:10.1016/j.echo.2023.02.007.

Francis JR, Whalley GA, Kaethner A, Fairhurst H, Hardefeldt H, Reeves B, Auld B, Marangou J, Horton A, Wheaton G, et al. 2021. Single-view echocardiography by nonexpert practitioners to detect rheumatic heart disease: a prospective study of diagnostic accuracy. Circ Cardiovasc Imaging. 14(8):e011790. doi:10.1161/CIRCIMAGING.120.011790.

Fulurija A, Cunningham MW, Korotkova N, Masterson MY, Bansal GP, Baker MG, Cannon JW, Carapetis JR, Steer AC. 2023. Research opportunities for the primordial prevention of rheumatic fever and rheumatic heart disease-streptococcal vaccine development: a national heart,

lung and blood institute workshop report. BMJ Glob Health. 8(Suppl 9):e013534. doi:10.1136/bmjgh-2023-013534.
Galvin JE, Hemric ME, Ward K, Cunningham MW. 2000. Cytotoxic mAb from rheumatic carditis recognizes heart valves and laminin. The Journal of Clinical Investigation. 106(2):217–224. doi:10.1172/JCI7132.
Gentles TL, Colan SD, Wilson NJ, Biosa R, Neutze JM. 2001. Left ventricular mechanics during and after acute rheumatic fever: contractile dysfunction is closely related to valve regurgitation. J Am Coll Cardiol. 37(1):201–207. doi:10.1016/S0735-1097(00)01058-5.
Gentles TL, Finucane AK, Remenyi B, Kerr AR, Wilson NJ. 2015. Ventricular function before and after surgery for isolated and combined regurgitation in the young. The Annals of Thoracic Surgery. 100(4):1383–1389. doi:10.1016/j.athoracsur.2015.06.009.
Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. 2020. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clinic Proceedings. 95:1213–1221. doi:10.1016/j.mayocp.2020.03.024.
Gunther G, Amsmera J, Parry E. 2006. Death from rheumatic heart disease in rural Ethiopia. The Lancet. 367:391. doi:10.1016/S0140-6736(06)68128-2.
Gurney J, Chong A, Culliford-Semmens N, Tilton E, Wilson NJ, Sarfati D. 2016. The benefits and harms of rheumatic heart disease screening from the perspective of the screened population. Int J Cardiol. 221:734–740. doi:10.1016/j.ijcard.2016.07.025.
Gurney JK, Chong A, Culliford-Semmens N, Tilton E, Wilson NJ, Sarfati D. 2017. High levels of rheumatic fever and sore throat awareness among a high-risk population screened for rheumatic heart disease. N Z Med J. 130(1450):107–110.
He Kāinga Oranga–Housing and Health. 2022. Improving housing quality and health outcomes in Aotearoa New Zealand. Newton, Wellington: He Kāinga Oranga–Housing and Health Research Programme; [accessed 2023]. https://www.healthyhousing.org.nz/.
Houkamau CA, Sibley CG. 2015. Looking Māori predicts decreased rates of home ownership: institutional racism in housing based on perceived appearance. PLoS One. 10(3):e0118540. doi:10.1371/journal.pone.0118540.
Illingworth RS, Burke J, Doxiadis SA, Lorber J, Philpott MG, Stone DG. 1954. Salicylates in rheumatic fever: an attempt to assess their value. Quarterly Journal of Medicine. 23(90):177–213.
Jack SJ, Williamson DA, Galloway Y, Pierse N, Zhang J, Oliver J, Milne RJ, Mackereth G, Jackson CM, Steer AC, et al. 2018. Primary prevention of rheumatic fever in the 21st century: evaluation of a national programme. Int J Epidemiol. 47(5):1585–1593. doi:10.1093/ije/dyy150.
Kado JH, Salman S, Henderson R, Hand R, Wyber R, Page-Sharp M, Batty K, Carapetis J, Manning L. 2020. Subcutaneous administration of benzathine benzylpenicillin G has favourable pharmacokinetic characteristics for the prevention of rheumatic heart disease compared with intramuscular injection: a randomized, crossover, population pharmacokinetic study in healthy adult volunteers. J Antimicrob Chemother. 75(10):2951–2959. doi:10.1093/jac/dkaa282.
Karacan M, Isikay S, Olgun H, Ceviz N. 2010. Asymptomatic rhythm and conduction abnormalities in children with acute rheumatic fever: 24-hour electrocardiography study. Cardiol Young. 20(6):620–630. doi:10.1017/S104795111000079X.
Karthikeyan G. 2016. Measuring and reporting disease progression in subclinical rheumatic heart disease. Heart Asia. 8(2):74–75. doi:10.1136/heartasia-2016-010857.
Karthikeyan G, Fung E, Foo RS. 2020. Alternative hypothesis to explain disease progression in rheumatic heart disease. Circulation. 142(22):2091–2094. doi:10.1161/CIRCULATIONAHA.120.050955.
Kim ML, Martin WJ, Minigo G, Keeble JL, Garnham AL, Pacini G, Smyth GK, Speed TP, Carapetis J, Wicks IP. 2018. Dysregulated IL-1beta-GM-CSF axis in acute rheumatic fever that is limited by hydroxychloroquine. Circulation. 138(23):2648–2661. doi:10.1161/CIRCULATIONAHA.118.033891.
Lacey JA, Bennett J, James TB, Hines BS, Chen T, Lee D, Sika-Paotonu D, Anderson A, Harwood M, Tong SYC, et al. 2024. A worldwide population of streptococcus pyogenes strains circulating

among school-aged children in Auckland, New Zealand: a genomic epidemiology analysis. The Lancet Reg Health West Pac. 42:100964.
Lennon D, Stewart J, Farrell E, Palmer A, Mason H. 2009. School-based prevention of acute rheumatic fever: a group randomized trial in New Zealand. Pediatr Infect Dis J. 28(9):787–794. doi:10.1097/INF.0b013e3181a282be.
Loh JMS, Rivera-Hernandez T, McGregor R, Khemlani AHJ, Tay ML, Cork AJ JMR, Moreland NJ, Walker MJ, Proft T. 2021. A multivalent T-antigen-based vaccine for Group A Streptococcus. Sci Rep. 11(1):4353. doi:10.1038/s41598-021-83673-4.
Lorenz N, Ho TKC, McGregor R, Davies MR, Williamson DA, Gurney JK, Smeesters PR, Baker MG, Moreland NJ. 2021. Serological profiling of group A Streptococcus infections in acute rheumatic fever. Clin Infect Dis. 73(12):2322–2325. doi:10.1093/cid/ciab180.
Macleod CK, Bright P, Steer AC, Kim J, Mabey D, Parks T. 2019. Neglecting the neglected: the objective evidence of underfunding in rheumatic heart disease. Trans R Soc Trop Med Hyg. 113:287–290. doi:10.1093/trstmh/trz014.
Malcolm J, Ball S, Beharry J, Seal RI, Lowe L, Biddle S, Wana L, Bennett M, Godfrey J. 2013. Tautoko rheumatic hearts: to support those with rheumatic hearts, public health needs innovation, collaboration and evaluation. In: Zander A, Came H, editors. Proceedings of the 2013 Public Health Association Conference, New Plymouth, Taranaki. Auckland, New Zealand: Public Health Association; p. 107–112.
Malo I, Paka J, Kailawadoko J, Pal P, Harihiru Kora'ai M, Tukana-Thaggard M, Saumi J, Raihman E, Bi E, Kado J. 2023. Integrating echo screening into the school health nurse visits in primary schools in Fiji islands. Wolrd Congress on Rheumatic Heart Disease. Abu Dhabi. p182.
Marijon E, Ou P, Celermajer DS, Ferreira B, Mocumbi AO, Jani D, Paquet C, Jacob S, Sidi D, Jouven X. 2007. Prevalence of rheumatic heart disease detected by echocardiographic screening. N Engl J Med. 357(5):470–476. doi:10.1056/NEJMoa065085.
McGregor R, Tay ML, Carlton LH, Hanson-Manful P, Raynes JM, Forsyth WO, Brewster DT, Middleditch MJ, Bennett J, Martin WJ, et al. 2021. Mapping autoantibodies in children with acute rheumatic fever. Front Immunol. 12:702877. doi:10.3389/fimmu.2021.702877.
Middleton FM, McGregor R, Webb RH, Wilson NJ, Moreland NJ. 2022. Cytokine imbalance in acute rheumatic fever and rheumatic heart disease: mechanisms and therapeutic implications. Autoimmun Rev. 21(12):103209. doi:10.1016/j.autrev.2022.103209.
Milne RJ, Lennon D, Stewart JM, Vander Hoorn S, Scuffham PA. 2012. Mortality and hospitalisation costs of rheumatic fever and rheumatic heart disease in New Zealand. Journal of Paediatrics and Child Health. 48(8):692–697. doi:10.1111/j.1440-1754.2012.02446.x.
Ministry of Health – Manatū Hauora. 2011. Rapide: rheumatic fever: a systematic review of the literature on health literacy, overcrowding and rheumatic fever. Wellington: New Zealand Guidelines Group.
Mirabel M, Bacquelin R, Tafflet M, Robillard C, Huon B, Corsenac P, de Fremicourt I, Narayanan K, Meunier JM, Noel B, et al. 2015. Screening for rheumatic heart disease: evaluation of a focused cardiac ultrasound approach. Circulation Cardiovascular Imaging. 8(1):e002324. doi:10.1161/CIRCIMAGING.114.002324.
Mirzoev T, Kane S. 2017. What is health systems responsiveness? Review of existing knowledge and proposed conceptual framework. BMJ Glob Health. 2(4):e000486. doi:10.1136/bmjgh-2017-000486.
Mitchell AG, Diddo J, James AD, Guraylayla L, Jinmarabynana C, Carter A, Rankin SD, Djorlom G, Coleman C, Scholes M, et al. 2021. Using community-led development to build health communication about rheumatic heart disease in aboriginal children: a developmental evaluation. Aust N Z J Public Health. 45(3):212–219. doi:10.1111/1753-6405.13100.
Moreland NJ, Waddington CS, Williamson DA, Sriskandan S, Smeesters PR, Proft T, Steer AC, Walker MJ, Baker EN, Baker MG, et al. 2014. Working towards a group A streptococcal vaccine: report of a collaborative Trans-Tasman workshop. Vaccine. 32(30):3713–3720. doi:10.1016/j.vaccine.2014.05.017.
Nascimento BR, Beaton AZ, Nunes MC, Diamantino AC, Carmo GA, Oliveira KK, Oliveira CM, Meira ZM, Castilho SR, Lopes EL, et al. 2016. Echocardiographic prevalence of rheumatic heart

disease in Brazilian schoolchildren: data from the PROVAR study. Int J Cardiol. 219:439–445. doi:10.1016/j.ijcard.2016.06.088.

Nascimento BR, Sable C, Nunes MCP, Oliveira KKB, Franco J, Barbosa MM, Reese AT, Diamantino AC, Ferreira Filho DSG, Macedo FVB, et al. 2021. Echocardiographic screening of pregnant women by non-physicians with remote interpretation in primary care. Fam Pract. 38(3):225–230. doi:10.1093/fampra/cmaa115.

National Advisory Committee on Health and Disability. 2003. Screening to improve health in New Zealand: criteria to assess screening programmes 2003: [1-49]. Wellington: National Health Committee; [accessed 2023]. http://nhc.health.govt.nz/.

Neves EGA, Koh CC, Padilha da Silva JL, Passos LSA, Villani FNA, Dos Santos JSC, Menezes CAS, Silva VR, Tormin J, Evangelista GFB, et al. 2021. Systemic cytokines, chemokines and growth factors reveal specific and shared immunological characteristics in infectious cardiomyopathies. Cytokine. 148:155711. doi:10.1016/j.cyto.2021.155711.

Newman JE, Lennon DR, Wong-Toi W. 1984. Patients with rheumatic fever recurrences. New Zealand Medical Journal. 97(765):678–680.

New Zealand Heart Foundation. 2014. New Zealand guidelines for rheumatic fever: diagnosis, management and secondary prevention of acute rheumatic fever and rheumatic heart disease: 2014 update. https://www.heartfoundation.org.nz/resources/acute-rheumatic-fever-and-rheumatic-heart-disease-guideline.

Okello E, Mordi IR, Lang CC, Sable C, Dougherty S, Wilson N. 2019. Chapter 6–Medical management of rheumatic heart disease. In: Dougherty S, Carapetis J, Zühlke L, Wilson N, editors. Acute rheumatic fever and rheumatic heart disease. San Diego, CA: Elsevier; p. 107–132.

Okello E, Ndagire E, Muhamed B, Sarnacki R, Murali M, Pulle J, Atala J, Bowen AC, DiFazio MP, Nakitto MG, et al. 2021. Incidence of acute rheumatic fever in northern and western Uganda: a prospective, population-based study. Lancet Glob Health. 9(10):e1423–e1430. doi:10.1016/S2214-109X(21)00288-6.

Oliver J, Bennett J, Thomas S, Zhang J, Pierse N, Moreland NJ, Williamson DA, Jack S, Baker M. 2021a. Preceding group A streptococcus skin and throat infections are individually associated with acute rheumatic fever: evidence from New Zealand. BMJ Glob Health. 6(12):e007038. doi:10.1136/bmjgh-2021-007038.

Oliver J, Robertson O, Zhang J, Marsters BL, Sika-Paotonu D, Jack S, Bennett J, Williamson DA, Wilson N, Pierse N, et al. 2021b. Ethnically disparate disease progression and outcomes among acute rheumatic fever patients in New Zealand, 1989-2015. Emerg Infect Dis. 27(7):1893–1902. doi:10.3201/eid2707.203045.

Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2021. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation. 143(5):e72–e227.

Otto H, Saether SG, Banteyrga L, Haugen BO, Skjaerpe T. 2011. High prevalence of subclinical rheumatic heart disease in pregnant women in a developing country: an echocardiographic study. Echocardiography. 28(10):1049–1053. doi:10.1111/j.1540-8175.2011.01520.x.

Parks T, Kado J, Miller AE, Ward B, Heenan R, Colquhoun SM, Barnighausen TW, Mirabel M, Bloom DE, Bailey RL, et al. 2015. Rheumatic heart disease-attributable mortality at ages 5–69 years in Fiji: a five-year, national, population-based record-linkage cohort study. PLoS Negl Trop Dis. 9(9):e0004033. doi:10.1371/journal.pntd.0004033.

Peck D, Rwebembera J, Nakagaayi D, Minja NW, Ollberding NJ, Pulle J, Klein J, Adams D, Martin R, Koepsell K, et al. 2023. The use of artificial intelligence guidance for rheumatic heart disease screening by novices. J Am Soc Echocardiogr. 36(7):724–732. doi:10.1016/j.echo.2023.03.001.

Perelini F, Agnew J, Skinner JR, Han DY, Nicholson R, Wilson N. 2022. Revisiting QT prolongation in acute rheumatic fever–relevance for hydroxychloroquine treatment. International Journal of Cardiology. 362:93–96. doi:10.1016/j.ijcard.2022.05.053.

Perelini F, Blair N, Wilson N, Farrell A, Aitken A. 2015. Family acceptability of school-based echocardiographic screening for rheumatic heart disease in a high-risk population in New Zealand. J Paediatr Child Health. 51(7):682–688. doi:10.1111/jpc.12829.

Ploutz M, Lu JC, Scheel J, Webb C, Ensing GJ, Aliku T, Lwabi P, Sable C, Beaton A. 2016. Handheld echocardiographic screening for rheumatic heart disease by non-experts. Heart. 102(1):35–39. doi:10.1136/heartjnl-2015-308236.

Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, et al. 2016. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 37(27):2129–2200. doi:10.1093/eurheartj/ehw128.

Ponticelli C, Moroni G. 2017. Hydroxychloroquine in systemic lupus erythematosus (SLE). Expert Opinion on Drug Safety. 16(3):411–419. doi:10.1080/14740338.2017.1269168.

Ralph AP, Webb R, Moreland NJ, McGregor R, Bosco A, Broadhurst D, Lassmann T, Barnett TC, Benothman R, Yan J, et al. 2021. Searching for a technology-driven acute rheumatic fever test: the START study protocol. BMJ Open. 11(9):e053720. doi:10.1136/bmjopen-2021-053720.

Reid P, Cormack D, Paine SJ. 2019. Colonial histories, racism and health-the experience of Māori and indigenous peoples. Public Health. 172:119–124. doi:10.1016/j.puhe.2019.03.027.

Remenyi B, Carapetis J, Stirling JW, Ferreira B, Kumar K, Lawrenson J, Marijon E, Mirabel M, Mocumbi AO, Mota C, et al. 2019. Inter-rater and intra-rater reliability and agreement of echocardiographic diagnosis of rheumatic heart disease using the world heart federation evidence-based criteria. Heart Asia. 11(2):e011233. doi:10.1136/heartasia-2019-011233.

Remenyi B, Davis K, Draper A, Bayley N, Paratz E, Reeves B, Appelbe A, Wheaton G, da Silva Almeida IT, Dos Santos J, et al. 2020. Single parasternal-long-axis-view-sweep screening echocardiographic protocol to detect rheumatic heart disease: a prospective study of diagnostic accuracy. Heart Lung Circ. 29(6):859–866. doi:10.1016/j.hlc.2019.02.196.

Remenyi B, Webb R, Gentles T, Russell P, Finucane K, Lee B, Wilson N. 2013a. Improved long-term survival for rheumatic mitral valve repair compare to replacement in the young. World Journal for Pediatric and Congenital Heart Surgery. 4(2):155–164. doi:10.1177/2150135112474024.

Remenyi B, Wilson N, Steer A, Ferreira B, Kado J, Kumar K, Lawrenson J, Maguire G, Marijon E, Mirabel M, et al. 2013b. World heart federation criteria for echocardiographic diagnosis of rheumatic heart disease-an evidence-based guideline. Nature Reviews Cardiology. 9(5):297–309. doi:10.1038/nrcardio.2012.7.

RHDAustralia (ARF/RHD writing group). 2020. The 2020 Australian Guideline for the Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease. https://www.rhdaustralia.org.au/system/files/fileuploads/arf_rhd_guidelines_3.2_edition_march_2022.pdf.

Rheumatic Fever Working Party. 1965. The natural history of rheumatic fever and rheumatic heart disease. Ten-year report of a cooperative clinical trial of ACTH, cortisone, and aspirin. A joint report by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association. Circulation. 32(3):457–476. doi:10.1161/01.CIR.32.3.457.

Roberts K, Brown A, Maguire G, Atkinson D, Carapetis J. 2013. Utility of auscultatory screening for detecting rheumatic heart disease in high-risk children in Australia's Northern Territory. Medical Journal of Australia. 199:196–199. doi:10.5694/mja13.10520.

Roberts K, Maguire G, Brown A, Atkinson D, Remenyi B, Wheaton G, Kelly A, Kumar RK, Su JY, Carapetis JR. 2014. Echocardiographic screening for rheumatic heart disease in high and low risk Australian children. Circulation. 129(19):1953–1961. doi:10.1161/CIRCULATIONAHA.113.003495.

Roberts S, Kosanke S, Terrence Dunn S, Jankelow D, Duran CM, Cunningham MW. 2001. Pathogenic mechanisms in rheumatic carditis: focus on valvular endothelium. The Journal of Infectious Diseases. 183(3):507–511. doi:10.1086/318076.

Roden DM, Harrington RA, Poppas A, Russo AM. 2020. Considerations for drug interactions on QTc in exploratory COVID-19 treatment. Circulation. 141(24):e906–e907. doi:10.1161/CIRCULATIONAHA.120.047521.

Rokovunisei M, Sakumeni K, Wheeler M, Matanaicake S, Lee R, Kailawadoko J, Ratu A, Kora'ai J, Savea S, Mow M, et al. 2023. Fiji antenatal echocardiography screening (fans) for rheumatic heart disease by trained non-expert health personnel. Wolrd Congress on Rheumatic Heart Disease. Abu Dhabi. 171.

Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al. 2020. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. J Am Coll Cardiol. 76(25):2982–3021. doi:10.1016/j.jacc.2020.11.010.

Rwebembera J, Marangou J, Mwita J, Mocumbi A, Mota C, Okello E, Nascimento B, Thorup L, Beaton A, Kado J, et al. 2023. 2023 world heart federation guidelines for the echocardiographic diagnosis of rheumatic heart disease. Nat Rev Cardiol. doi:10.1038/s41569-023-00940-9.

Schodel F, Moreland NJ, Wittes JT, Mulholland K, Frazer I, Steer AC, Fraser JD, Carapetis J. 2017. Clinical development strategy for a candidate group A streptococcal vaccine. Vaccine. 35(16):2007–2014. doi:10.1016/j.vaccine.2017.02.060.

Schwaninger S, Musuku J, Engel ME, Musonda P, Lungu JC, Machila E, Mtaja A, Mulendele E, Kavindele D, Spector J, et al. 2018. Prevalence of rheumatic heart disease in Zambian school children. BMC Cardiovasc Disord. 18(1):135. doi:10.1186/s12872-018-0871-8.

Shippey EA, Wagler VD, Collamer AN. 2018. Hydroxychloroquine: an old drug with new relevance. Cleve Clin J Med. 85(6):459–467. doi:10.3949/ccjm.85a.17034.

Shukla AM, Archibald LK, Wagle Shukla A, Mehta HJ, Cherabuddi K. 2020. Chloroquine and hydroxychloroquine in the context of COVID-19. Drugs Context. 9:2020-2024-2025. doi:10.7573/dic.2020-4-5.

Spinetto H, Lennon D, Horsburgh M. 2011. Rheumatic fever recurrence prevention: a nurse-led programme of 28-day penicillin in an area of high endemnicity. Journal of Paediatrics and Child Health. 47(4):228–234. doi:10.1111/j.1440-1754.2010.01942.x.

Te Tūāpapa Kura Kāinga–Ministry of Housing and Urban Development. 2023. MAIHI Ka Ora – The National Māori Housing strategy. Wellington: Te Tūāpapa Kura Kāinga–Ministry of Housing and Urban Development; [accessed 2023]. https://www.hud.govt.nz/assets/Uploads/Documents/MAIHI-Ka-Ora-Strategy-Document.pdf; https://www.hud.govt.nz/our-work/maihi-ka-ora-the-national-maori-housing-strategy/.

Te Whatu Ora. 2023a. The Rheumatic Fever Prevention Programme (RFPP). Auckland, New Zealand: Te Whatu Ora, Health New Zealand; [accessed 2023 July 2023]. https://www.tewhatuora.govt.nz/for-the-health-sector/health-sector-guidance/diseases-and-conditions/rheumatic-fever-guidance/about/#the-rheumatic-fever-prevention-programme-rfpp.

Te Whatu Ora. 2023b. Rheumatic Fever Roadmap, 2023–2028. Auckland, New Zealand: Te Whatu Ora, Health New Zealand; [accessed 2023 July 2023]. https://www.tewhatuora.govt.nz/publications/rheumatic-fever-roadmap-2023-2028.

Tilton E, Mitchelson B, Anderson A, Peat B, Jack S, Lund M, Webb R, Wilson N. 2022. Cohort profile: methodology and cohort characteristics of the Aotearoa New Zealand rheumatic heart disease registry. BMJ Open. 12(12):e066232. doi:10.1136/bmjopen-2022-066232.

Tormin J, Nascimento BR, Sable CA, da Silva JLP, Brandao-de-Resende C, Rocha LPC, Pinto CHR, Neves EGA, Macedo FVB, Fraga CL, et al. 2021. Cytokine gene functional polymorphisms and phenotypic expression as predictors of evolution from latent to clinical rheumatic heart disease. Cytokine. 138:155370. doi:10.1016/j.cyto.2020.155370.

Trace AJ. 2022. Multisectoral and decolonial approaches to prevent acute rheumatic fever in Aotearoa [master's thesis]. Auckland: University of Auckland.

Tu'akoi S, Ofanoa M, Ofanoa S, Lutui H, Heather M, Jansen RM, Goodyear-Smith F. 2023. Addressing rheumatic fever inequities in Aotearoa New Zealand: a scoping review of prevention interventions. J Prim Health Care. 15(1):59–66. doi:10.1071/HC22093.

University of Auckland–Waipapa Taumata Rau. 2022. Rheumatic fever: time to stamp out this deadly and preventable disease. Auckland: University of Auckland–Waipapa Taumata Rau; [accessed 2023]. https://www.auckland.ac.nz/en/news/2022/03/29/rheumatic-fever-time-to-stamp-it-out.html.

Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. 2022. The global burden of cardiovascular diseases and risk: a compass for future health. J Am Coll Cardiol. 80(25):2361–2371. doi:10.1016/j.jacc.2022.11.005.

Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, et al. 2022. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 43(7):561–632. doi:10.1093/eurheartj/ehab395.

Voleti S, Adelbai M, Hovis I, Colyer J, Burns KM, Lewis EO, Arurang JK, Kikuharu A, Gonzales M, Pedro SJ, et al. 2021. Novel handheld ultrasound technology to enhance non-expert screening for rheumatic heart disease in the Republic of Palau: a descriptive study. J Paediatr Child Health. 57(7):1089–1095. doi:10.1111/jpc.15409.

Voss LM, Wilson NJ, Neutze JM, Whitlock RM, Ameratunga RV, Cairns LM, Lennon DR. 2001. Intravenous immunoglobulin in acute rheumatic fever: a randomized controlled trial. Circulation. 103(3):401–406. doi:10.1161/01.CIR.103.3.401.

Waitangi Tribunal-Te Rōpū Whakamana i te Tiriti o Waitangi. 2020. Housing policy and services inquiry. The Terrace, Wellington: Ministry of Justice; [accessed 2023]. https://www.waitangitribunal.govt.nz/claims-process/.

Walkinshaw DR, Wright MEE, Mullin AE, Excler JL, Kim JH, Steer AC. 2023. The streptococcus pyogenes vaccine landscape. NPJ Vaccines. 8(1):16. doi:10.1038/s41541-023-00609-x.

Wark EK, Hodder YC, Woods CE, Maguire GP. 2013. Patient and health-care impact of a pilot rheumatic heart disease screening program. J Paediatr Child Health. 49(4):297–302. doi:10.1111/jpc.12154.

Webb R. 2019. Rheumatic heart disease in New Zealand children: echocardiographic disease burden and clinical outcomes [master's thesis]. Auckland: University of Auckland.

Webb R, Culliford-Semmens N, ChanMow A, Doughty R, Tilton E, Peat B, Stirling J, Gentles TL, Wilson NJ. 2023. High burden of rheumatic heart disease confirmed by echocardiography among pacific adults living in New Zealand. Open Heart. 10(1):e002253. doi:10.1136/openhrt-2023-002253.

Webb RH, Culliford-Semmens N, Sidhu K, Wilson NJ. 2017. Normal echocardiographic mitral and aortic valve thickness in children. Heart Asia. 9(1):70–75. doi:10.1136/heartasia-2016-010872.

Webb RH, Gentles TL, Stirling JW, Lee M, O'Donnell C, Wilson NJ. 2015. Valvular regurgitation using portable echocardiography in a healthy student population: implications for rheumatic heart disease screening. J Am Soc Echocardiogr. 28(8):981–988. doi:10.1016/j.echo.2015.03.012.

Webb RH, Wilson NJ, Lennon DR, Wilson EM, Nicholson RW, Gentles TL, O'Donnell CP, Stirling JW, Zeng I, Trenholme AA. 2011. Optimising echocardiographic screening for rheumatic heart disease in New Zealand: not all valve disease is rheumatic. Cardiol Young. 21(4):436–443. doi:10.1017/S1047951111000266.

Whitcombe AL, McGregor R, Bennett J, Gurney JK, Williamson DA, Baker MG, Moreland NJ. 2022. Increased breadth of group A Streptococcus antibody responses in children with acute rheumatic fever compared to precursor pharyngitis and skin infections. J Infect Dis. 226(1):167–176. doi:10.1093/infdis/jiac043.

White A. 2018. WHO resolution on rheumatic heart disease. Eur Heart J. 39(48):4233. doi:10.1093/eurheartj/ehy764.

WHO. 2018. Rheumatic heart disease. Geneva, Switzerland: World Health Organization; [accessed 2023 August]. https://www.who.int/news-room/fact-sheets/detail/rheumatic-heart-disease#:~:text=In%202018%2C%20the%20World%20Health,heart%20disease%20and%20rheumatic%20fever.

Wilson N. 2008. Echocardiography and subclinical carditis: guidelines that increase sensitivity for acute rheumatic fever. Cardiology in the Young. 18(6):565–568. doi:10.1017/S1047951108003211.

Wilson N. 2013. Secondary prophylaxis for rheumatic fever: simple concepts, difficult delivery. World Journal for Pediatric & Congenital Heart Surgery. 4(4):380–384. doi:10.1177/2150135113497240.

Wilson NJ, Concannon A, Malcolm J, Davidakova S, Martin WJ, Webb R, Moreland NJ. 2020. The treatment of acute rheumatic fever: novel use of hydroxychloroquine. Pediatr Infect Dis J. 39(7): e120–e122. doi:10.1097/INF.0000000000002647.

Wilson NJ, Neutze JM. 1995. Echocardiographic diagnosis of subclinical carditis in acute rheumatic fever. Int J Cardiol. 50(1):1–6. doi:10.1016/0167-5273(95)02325-Q.

Wilson NJ, Voss L, Morreau J, Stewart J, Lennon D. 2013. New Zealand guidelines for the diagnosis of acute rheumatic fever: small increase in the incidence of definite cases compared to the American heart association jones criteria. New Zealand Medical Journal. 126(1379):50–59.

Wilson NJ, Voss LM, Neutze JM, Ameratunga RV, Lennon DR. 1997. The natural history of acute rheumatic fever to one year in the echocardiographic era. Proceedings of the 2nd World Congress of Paediatric Cardiology and Cardiac Surgery. Hawaii, USA. NZ. 971–972.

World Health Organisation. 2007. Task shifting: global recommendations and guidelines. Geneva, Switzerland: World Health Organisation; [accessed]. https://www.unaids.org/sites/default/files/media_asset/ttr_taskshifting_en_0.pdf.

Wyber R, Bowen AC, Ralph AP, Peiris D. 2021a. Primary prevention of acute rheumatic fever. Aust J Gen Pract. 50(5):265–269. doi:10.31128/AJGP-02-21-5852.

Wyber R, Wade V, Anderson A, Schreiber Y, Saginur R, Brown A, Carapetis J. 2021b. Rheumatic heart disease in indigenous young peoples. The Lancet Child & Adolescent Health. 5(6):437–446. doi:10.1016/S2352-4642(20)30308-4.

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, et al. 2017. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart failure society of America. J Card Fail. 23(8):628–651. doi:10.1016/j.cardfail.2017.04.014.

Zhang W, Okello E, Nyakoojo W, Lwabi P, Mondo CK. 2015. Proportion of patients in the Uganda rheumatic heart disease registry with advanced disease requiring urgent surgical interventions. Afr Health Sci. 15(4):1182–1188. doi:10.4314/ahs.v15i4.17.

Zilla P, Yacoub M, Zuhlke L, Beyersdorf F, Sliwa K, Khubulava G, Bouzid A, Mocumbi AO, Velayoudam D, Shetty D, et al. 2018. Global unmet needs in cardiac surgery. Glob Heart. 13 (4):293–303. doi:10.1016/j.gheart.2018.08.002.